Amendments to the Specification

Please replace Paragraph **[059]** appearing on page 11 of the Specification with the following replacement paragraph:

All synthetic oligonucleotide primers for PCR were by Biotech. The sense primer pET5 5'_[[°]]AGATCTCGATCCCGCGAAATTAATACG [[°]]3'_ (SEQ ID NO: 1) and the antisense primer pET3 5'_[[°]] CAAAAAACCCCTCAAGACCCGTTTAG[[°]]3' (SEQ ID NO: 2) (with or without phosphorothioate (PTO) termination) were used to amplify the GFP gene (GENBANK : AEVGFP) pET26b+ cloned (Figure 4) and make phosphorothioate sense and/or antisense strand.

Please replace paragraph **[041]** appearing on page 8 of the Specification with the following replacement paragraph:

Fig. 4 depicts a plasmid map of PET26GFP ~~preparation of ssDNA and a parental template~~.

Please replace paragraph **[042]** appearing on page 8 of the Specification with the following replacement paragraph:

Fig. 5 depicts the results of specific ssDNA preparation using specific lambda exonuclease digestion conditions.

Please replace paragraph **[043]** appearing on page 8 of the Specification with the following replacement paragraph:

Fig. 6 depicts ssDNA preparation using specific lambda exonuclease the results of specific digestion conditions.

Please replace paragraph **[045]** appearing on page 8 of the Specification with the following replacement paragraph:

Fig. 8 depicts PCR [[PGR]] amplification.

Please replace paragraph **[020]** appearing on page 4 to page 5 of the Specification with the following replacement paragraph:

The phrase "at least two homologous heteroduplex polynucleotides" refers to a plurality of double-stranded polynucleotides, wherein a strand of each double-stranded polynucleotide is [[are]] not only imperfectly complementary to its opposed strand, but also differs ~~differa~~ from the corresponding strand of one of the other double-stranded polynucleotides at least at one

corresponding residue position. In other words, the heteroduplex polynucleotides are homologous to each other.

Please replace paragraph **[009]** appearing on page 3 of the Specification with the following replacement paragraph:

The MMR pathway continues with the MutS binding to mismatched base pairs. See Figure 3. MutL is then recruited to the complex and activates MutH which binds to GATC sequences. Activation of MutH cleaves the unmethylated strand at a GATC site. Subsequently, the segment from the cleavage site to the mismatch is removed by exonuclease. This step simultaneously involves helicase II and single strand ~~strain~~ DNA binding proteins. These single strand ~~strain~~ DNA binding proteins are called SSB proteins. If the cleavage occurs on the 3' side of the mismatch, the step is carried out by exonuclease I (which degrades a single strand only in the 3' to 5' direction). If the cleavage occurs on the 5' side of the mismatch, exonuclease VII or RecJ is used to degrade the single stranded DNA. The gap is filled by DNA polymerase III and DNA ligase. The distance between the GATC site and the mismatch can be as long as 1000 base pairs. Therefore, mismatch repair is very expensive and inefficient.

Please replace paragraph **[008]** appearing on page 2 to page 3 of the Specification with the following replacement paragraph:

In the MMR pathway, the involved proteins in E. coli are DAM methylase, MutS, MutL, MutH, exonuclease, DNA helicase II, SSB protein, DNA polymerase III and DNA ligase. To repair mismatched bases, the pathway involves a determination of which base is the correct one. In E. coli, this determination is achieved by a special methylase called Dam methylase, which can methylate all adenines that occur within (5')GATC sequences. Immediately after DNA replication, the template strand has been methylated, but the newly synthesized strand has not yet been methylated. Thus, the template strand and the new strand can be distinguished. Mismatch repair in eukaryotes may be similar to that in E. coli. Homologs of MutS and MutL have been identified in yeast, mammals, and other eukaryotes. MSHl to MSH5 are homologous to MutS. MLHl, PMSI and PMS2 are homologous to MutL. In eukaryotes ~~eukaiyotes~~, the mechanism to distinguish the template strand from the new strand is still unclear.

Please replace paragraph **[048]** appearing on page 9 of the Specification with the following replacement paragraph:

In another embodiment, the present invention provides a method and process of forming fragments which can be used with any shuffling process or combination of shuffling processes. In a further preferred embodiment, a library of mutants from an original gene or family of genes is used as a substrate or substrates for steps comprising denaturing and hybridization. The original gene may be obtained by mutagenic PCR, error-prone ~~enor-prone~~ PCR, chemical mutagenesis, physical mutagenesis, or a combination thereof. In another preferred embodiment, the step comprising hybridization further comprises creation of heteroduplexes and

homoduplexes. The heteroduplexes may then be used after mismatch recognition as substrate or substrates for fragment preparation.

Please replace paragraph **[058]** appearing on page 11 of the Specification with the following replacement paragraph:

This example depicts the preparation of ss DNA and a parental template.

I. MATERIALS AND METHODS

A. Oligonucleotides ~~Olitronucleotides~~

Please replace paragraph **[069]** appearing on page 13 of the Specification with the following replacement paragraph:

A PCR amplification of the GFP gene was achieved starting from pET26GFP (compare with Figure 4) and using 5 PGFP/3 GFPPTO. 1 gram of PCR product resulting from the amplification of GFP gene using pET26GFP as template was then treated with 8 U of dam methylase in order to methylate two specific dam methylase sites GATC as shown in Figure 7.

Please replace paragraph **[063]** appearing on page 12 of the Specification with the following replacement paragraph:

These PCR products were then incubated with or without lambda exonuclease for a selective digestion of 5' [[5]] P strands, as shown in Figure 5. Condition (1) resulted in a total lambda exonuclease digestion of pET5 P/pET3 P amplification (see lane B, Figure 5) compared to the undigested experimental conditions of the same PCR product (see lane A, Figure 5). Condition (2) resulted in no digestion of PET5 PTO/pET3 PTO amplification (see lane C, Figure 5). Condition (3) resulted in a selective digestion of anti-sense strand resulting in a ss DNA template (see lane D, Figure 5). Condition (4) resulted in a selective digestion of sense strand resulting in a ss DNA polynucleotides as shown in white (Figure 6).

Please replace paragraph **[068]** appearing on page 13 of the Specification with the following replacement paragraph:

Fragmentation assays were carried out in 20 liters [[l]] containing 0.02 M Tris-HCl (pH 7.6); 5[[°]]mM $MgCl_2$; 40 grams bovine serum albumin; 1 mM ATP; an appropriate concentration of each purified MMR proteins and 100 fmol of heteroduplexes. Incubation was achieved at 37°C for 1 hour and 30 liters [[1]]of 25 mM EDTA (pH 8.0) was then added. The DNA was purified by phenol extraction and ethanol precipitation. The resuspended DNA was then analyzed on denaturing 1 % agarose gel.